

AMENDMENT TO THE CLAIMS

The present document amends claims 4, 24, 68, 70, 71, 73, 75-77 and 80-82, and adds claim 89. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the status of the claims in the case is as follows:

Claims 1-3 canceled

4. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first antibody, or antigen-binding fragment thereof, kills at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promotes

coagulation in at least a portion of the blood vessels of the vascularized tumor, destroys or occludes at least a portion of the blood vessels of the vascularized tumor, induces necrosis in at least a portion of the tumor, induces tumor regression or induces tumor remission.

5. (Previously Presented) The method of claim 4, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine of a phosphatidylethanolamine-protein complex on the luminal surface of blood vessels of the vascularized tumor.

6. (Previously Presented) The method of claim 4, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine of a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor.

7. (Previously Presented) The method of claim 4, wherein said at least a first antibody is an IgG or IgM anti-aminophospholipid antibody.

8. (Previously Presented) The method of claim 4, wherein said at least a first antigen-binding fragment of an antibody is an scFv, Fv, Fab', Fab or F(ab')₂ antigen-binding fragment of an anti-aminophospholipid antibody.

9. (Previously Presented) The method of claim 4, wherein said at least a first antibody is a human, humanized or part-human chimeric anti-aminophospholipid antibody or antigen-binding fragment thereof.

Claim 10 canceled

Claims 11-22 canceled

23. (Previously Presented) The method of claim 4, wherein said at least a first antibody is a dimer, trimer or multimer of an anti-aminophospholipid antibody or antigen-binding fragments thereof.

24. (Currently Amended) ~~The method of claim 4, wherein at least a second antibody that binds to an aminophospholipid of an aminophospholipid-protein complex, or an antigen-binding fragment thereof, is administered to said animal~~ A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first and second antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

25. (Previously Presented) The method of claim 4, wherein said at least a first pharmaceutical composition is administered to said animal via intravenous administration.

26. (Original) The method of claim 4, wherein an image of the vasculature of said vascularized tumor is first obtained by administering to said animal a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to and identifies an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.

27. (Original) The method of claim 4, further comprising subjecting said animal to surgery or radiotherapy.

Claims 28-40 canceled

41. (Original) The method of claim 4, wherein said animal is a human patient.

Claims 42-48 canceled

49. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B.

50. (Previously Presented) The method of claim 49, wherein said at least a second therapeutic agent is carmustine, cytosine arabinoside, methotrexate, aminopterin, demecolcine, mithramycin, chlorambucil, melphalan, daunorubicin, doxorubicin, verapamil, tamoxifen, taxol, vincristine, vinblastine, etoposide, 5-fluorouracil (5FU), camptothecin, actinomycin-D, mitomycin C, cisplatin, a combretastatin or cyclophosphamide.

51. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C.

52. (Previously Presented) The method of claim 51, wherein said at least a second therapeutic agent is angiostatin or endostatin.

53. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is an inflammatory cytokine.

54. (Previously Presented) The method of claim 53, wherein said at least a second therapeutic agent is interleukin-4.

55. (Previously Presented) The method of claim 73, further comprising simultaneously or sequentially administering to said animal a therapeutically effective amount of at least a second therapeutic agent.

56. (Previously Presented) The method of claim 73, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine of a phosphatidylethanolamine-protein complex on the luminal surface of blood vessels of the vascularized tumor.

57. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is a compound that interferes with tubulin activity.

58. (Previously Presented) The method of claim 57, wherein said at least a second therapeutic agent is taxol, vincristine, vinblastine, bleomycin, or a combretastatin.

59. (Previously Presented) The method of claim 73, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine of a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor.

60. (Previously Presented) The method of claim 59, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine of a phosphatidylserine and β_2 -glycoprotein I complex on the luminal surface of blood vessels of the vascularized tumor.

61. (Previously Presented) The method of claim 4, wherein said at least a first antibody and said at least a second therapeutic agent are administered to said animal simultaneously.

62. (Previously Presented) The method of claim 4, wherein said at least a first antibody and said at least a second therapeutic agent are administered to said animal sequentially.

63. (Previously Presented) The method of claim 62, wherein said at least a second therapeutic agent is administered to said animal prior to said at least a first antibody.

64. (Previously Presented) The method of claim 63, wherein said at least a second therapeutic agent injures or induces apoptosis in the endothelium of the blood vessels of said vascularized tumor.

65. (Previously Presented) The method of claim 64, wherein said at least a second therapeutic agent is taxol, vincristine, vinblastine, neomycin, a combretastatin, a podophyllotoxin, TNF- α , angiostatin, endostatin, vasculostatin, an $\alpha_v\beta_3$ antagonist; or is a prodrug thereof.

66. (Previously Presented) The method of claim 62, wherein said at least a second therapeutic agent is administered to said animal subsequent to said at least a first antibody.

67. (Previously Presented) The method of claim 66, wherein said at least a second therapeutic agent is an anti-tumor cell immunotoxin or an anti-angiogenic agent.

68. (Currently Amended) A method for treating cancer, comprising simultaneously or sequentially administering to an animal having a vascularized tumor a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first

unconjugated antibody, or antigen-binding fragment thereof, that targets and binds to phosphatidylserine of a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first antibody, or antigen-binding fragment thereof, kills at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promotes coagulation in at least a portion of the blood vessels of the vascularized tumor, destroys or occludes at least a portion of the blood vessels of the vascularized tumor, induces necrosis in at least a portion of the tumor, induces tumor regression or induces tumor remission.

69. (Previously Presented) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first unconjugated antibody, or antigen-binding fragment thereof, that targets and binds to phosphatidylethanolamine on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

70. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first ~~seFv, Fv, Fab', Fab or F(ab')₂~~ antibody, or antigen-binding fragment of an antibody thereof, that targets and binds to ~~an aminophospholipid~~ phosphatidylethanolamine of ~~an aminophospholipid-protein~~ a phosphatidylethanolamine-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

71. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first ~~human, humanized or part-human-chimeric~~ antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first antibody, or antigen-binding fragment thereof, kills at least a portion of the endothelial cells of the blood vessels of the vascularized tumor.

72. (Previously Presented) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a tumor-destructive amount of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

73. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising administering to said animal ~~a therapeutically effective amount of at least a first pharmaceutical composition comprising~~ at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor in an amount effective to kill at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promote coagulation in at least a portion of the blood vessels of the vascularized tumor, destroy or occlude at least a portion of the blood vessels of the vascularized tumor, induce necrosis in at least a portion of the tumor, induce tumor regression or induce tumor remission.

74. (Previously Presented) A method for treating an animal having a vascularized tumor, comprising:

- (a) forming an image of the vasculature of said vascularized tumor by administering to said animal a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to and identifies an

aminophospholipid on the luminal surface of blood vessels of the vascularized tumor; and

- (b) simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:
 - (i) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
 - (ii) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
 - (iii) an inflammatory cytokine; or
 - (iv) a compound that interferes with tubulin activity.

75. (Currently Amended) A method for treating a ~~human patient~~ an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said ~~patient~~ animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first antibody, or antigen-binding fragment thereof, promotes coagulation in at least a portion of the blood vessels of the vascularized tumor.

76. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is ~~a compound that interferes with tubulin activity;~~

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first antibody, or antigen-binding fragment thereof, induces tumor regression.

77. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is ~~taxol, vincristine, vinblastine, bleomycin or a combretastatin;~~

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first antibody, or antigen-binding fragment thereof, induces tumor remission.

78. (Previously Presented) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a tumor necrosis-

inducing amount of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

79. (Previously Presented) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of tumor blood vessels of the vascularized tumor in an amount effective to destroy or occlude at least a portion of said tumor blood vessels; and at least a second therapeutic agent, wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;

- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

80. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent injures or induces apoptosis in the endothelium of the blood vessels of said vascularized tumor and wherein said at least a first antibody, or antigen-binding fragment thereof, kills at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promotes coagulation in at least a portion of the blood vessels of the vascularized tumor, destroys or occludes at least a portion of the blood vessels of the vascularized tumor, induces necrosis in at least a portion of the tumor, induces tumor regression or induces tumor remission.

81. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising ~~simultaneously or sequentially~~ administering to said animal a therapeutically effective ~~combination~~ amount of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid phosphatidylethanolamine of an ~~aminophospholipid-protein~~ a phosphatidylethanolamine-protein complex on the luminal surface of blood vessels of the vascularized tumor ~~and at least a second therapeutic agent; wherein said second therapeutic agent~~

~~is taxol, vincristine, vinblastine, neomycin, a combretastatin, a podophyllotoxin, TNF- α , angiostatin, endostatin, vasculostatin, an $\alpha_v\beta_3$ antagonist; or is a prodrug thereof.~~

82. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity;

and wherein said at least a first unconjugated antibody, or antigen-binding fragment thereof, kills at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promotes coagulation in at least a portion of the blood vessels of the vascularized tumor, destroys or occludes at least a portion of the blood vessels of the vascularized tumor, induces necrosis in at least a portion of the tumor, induces tumor regression or induces tumor remission.

83. (Previously Presented) The method of claim 4, wherein said at least a first antibody is an anti-aminophospholipid monoclonal antibody or antigen-binding fragment thereof.

84. (Previously Presented) The method of claim 4, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine of a phosphatidylserine and β_2 -glycoprotein I complex on the luminal surface of blood vessels of the vascularized tumor.

85. (Previously Presented) The method of claim 73, wherein said at least a first antibody is a monoclonal, human, humanized, part-human chimeric or trimeric anti-aminophospholipid antibody or an antigen-binding fragment thereof.

86. (Previously Presented) The method of claim 82, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine on the luminal surface of blood vessels of the vascularized tumor.

87. (Previously Presented) The method of claim 82, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine on the luminal surface of blood vessels of the vascularized tumor.

88. (Previously Presented) The method of claim 82, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor.

89. (New) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid of an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.